Elecsys Tg II

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REF		Σ	SYSTEM
08906564190* 08906564214*	08906564500	300	**cobas e** 402 **cobas e** 801

* Some kits shown may not be available in all countries.

English

System information

Short name	ACN (application code number)
TG 2	10215

Please note

Thyroglobulin (Tg) determinations can be affected by the presence of Tg autoantibodies (anti-Tg) in some patient samples. These autoantibodies may interfere with the assay used to measure Tg, causing false high or false low Tg values.[1,2]

The measured Tg value of a patient's sample can also vary depending on the assay used. The laboratory finding must therefore always contain a statement on the Tg assay method used. Tg values determined on patient samples by different assays cannot be directly compared with one another and could be the cause of erroneous medical interpretations. If there is a change in the Tg assay procedure used while patient monitoring, the Tg values obtained upon changing to the new procedure must be confirmed by parallel measurements with both methods.[2,3]

Intended use

Immunoassay for the in vitro quantitative determination of thyroglobulin in human serum and plasma. Determination of Tg is used as an aid in monitoring after thyroid ablation.

The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on **cobas e** immunoassay analyzers.

Summary

Thyroglobulin is a glycoprotein with a molecular weight of approximately 660 kDa.[4,5] Tg is synthesized in large quantities by the thyrocytes and released into the follicular lumen.[5,6]

Tg plays a decisive role in the synthesis of the peripheral thyroid hormones T3 and T4. It contains approximately 132 tyrosine residues, and around a third of these can be iodinated to monoiodo- and diiodothyrosine (MIT and DIT) in the presence of TPO (thyroid peroxidase) and iodide.[7,8] The subsequent coupling of MIT and DIT to form T3 and T4 also takes place on the Tg matrix with the involvement of TPO.[7,8,9]

Synthesis of T3 and T4 from Tg is regulated by TSH, intrathyroidal iodine levels and the presence of thyroid-stimulating immunoglobulins.[9,10,11]

During synthesis of Tg by the thyrocytes and the transport of Tg to the follicles, small quantities of the protein can pass into the bloodstream. Accordingly, low concentrations of Tg can be found in the blood of healthy individuals not suffering from thyroid diseases.[5]

Elevated Tg concentrations have been reported in many different thyroid conditions such as Hashimoto's disease, Graves' disease, thyroid adenoma, and thyroid carcinoma. The determination of Tg can also be helpful to distinguish between subacute thyroiditis and factitious thyrotoxicosis. In cases of congenital hypothyroidism the determination of Tg can be used to differentiate between the complete absence of the thyroid gland and thyroid hypoplasia or other pathological conditions.[12,13,14]

The main application of Tg testing is the post-operative follow-up of patients with differentiated thyroid carcinoma (DTC). A global rise in the prevalence of DTC has resulted in higher numbers of thyroidectomized patients who require lifelong monitoring for persistent or recurrent disease.[15,16] As the thyroid gland is the only known source of Tg, the serum Tg level will drop to a very low or undetectable concentration after total or near-total thyroidectomy and successful radioiodine ablation of the residual thyroid tissue. Detectable levels of serum Tg after total thyroidectomy are indicative of persistent or recurrent DTC. As a consequence significantly increasing Tg levels are interpreted as a sign of recurrence of the disease.[17,18,19,20,21,22]

In patients who have undergone a partial thyroidectomy Tg levels will still be measurable depending on how much tissue is remaining after surgery.

Detection of occult and early recurrence of disease has traditionally required Tg stimulation with high TSH concentrations. However, the development of highly sensitive assays allows Tg detection at very low concentrations without the need for stimulation.[16,23,24] Using these very sensitive Tg assays an increased number of 'thyroglobulin-positive' patients may be observed, even if patients show no clinical evidence of disease.[22] These patients cannot be defined as disease-free and should be monitored according to current guidelines. Different cutoff values are published to distinguish between monitoring patients and patients with recurrence of disease who need further diagnosis and treatment. Alternatively, institutional cutoff levels can be established to tailor the follow-up strategies to the local patient population and the thyroglobulin test used.[17,18,19,22]

All Tg results should be interpreted in conjunction with the total clinical presentation of the patient, including symptoms, clinical history, data from additional tests (i.e. neck ultrasound, whole body scan) and other appropriate information.

Tg determinations can be affected by the presence of Tg autoantibodies causing false high or false low Tg values. Therefore anti-Tg determinations are recommended for all Tg samples to rule out this interference.[1,2]

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: Tg from 21 µL of sample, a biotinylated monoclonal Tg-specific antibody and monoclonal Tg-specific antibodies labeled with a ruthenium complex[a)] react to form a sandwich complex.
- 2nd incubation: After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.
- The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell II M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the **cobas** link.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex ($Ru(bpy)_3^{2+}$)

Reagents - working solutions

The **cobas e** pack is labeled as TG 2.

M Streptavidin-coated microparticles, 1 bottle, 12.4 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-Tg-Ab~biotin, 1 bottle, 18.8 mL:
Biotinylated monoclonal anti-Tg antibody (mouse) 1 mg/L; Bis-Tris buffer 50 mmol/L, pH 6.3; preservative.

R2 Anti-Tg-Ab~$Ru(bpy)_3^{2+}$, 1 bottle, 18.8 mL:
Monoclonal anti-Tg antibodies (mouse) labeled with ruthenium complex 3.1 mg/L; Bis-Tris buffer 50 mmol/L, pH 6.3; preservative.

Precautions and warnings

For in vitro diagnostic use for health care professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste:
Warning: handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards:
Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

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Warning

H317 May cause an allergic skin reaction.

Prevention:

P261 Avoid breathing mist or vapours.

P272 Contaminated work clothing should not be allowed out of the workplace.

P280 Wear protective gloves.

Response:

P333 + P313 If skin irritation or rash occurs: Get medical advice/attention.

P362 + P364 Take off contaminated clothing and wash it before reuse.

Disposal:

P501 Dispose of contents/container to an approved waste disposal plant.

Product safety labeling follows EU GHS guidance.

Contact phone: all countries: +49-621-7590

Avoid foam formation in all reagents and sample types (specimens, calibrators and controls).

Reagent handling

The reagents in the kit have been assembled into a ready-for-use unit that cannot be separated.

All information required for correct operation is available via the **cobas** link.

Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the **cobas e** pack **upright** in order to ensure complete availability of the microparticles during automatic mixing prior to use.

Stability:	
unopened at 2-8 °C	up to the stated expiration date
on the analyzers	16 weeks

Specimen collection and preparation

Only the specimens listed below were tested and found acceptable.

Serum collected using standard sampling tubes or tubes containing separating gel.

Li-heparin, K_2-EDTA and K_3-EDTA plasma.

Plasma tubes containing separating gel can be used.

Criterion: Slope 0.9-1.1 + intercept within ≤ ± 0.04 ng/mL + coefficient of correlation ≥ 0.95.

Stable for 14 days at 15-25 °C, 14 days at 2-8 °C, 24 months at -20 °C (± 5 °C). Freeze only once.

The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

Centrifuge samples containing precipitates before performing the assay.

Do not use heat-inactivated samples.

Do not use samples and controls stabilized with azide.

Ensure the samples and calibrators are at 20-25 °C prior to measurement.

Due to possible evaporation effects, samples and calibrators on the analyzers should be analyzed/measured within 2 hours.

Materials provided

See “Reagents – working solutions” section for reagents.

Materials required (but not provided)

- REF 08991405190, Tg II CalSet, for 4 x 1.0 mL
- REF 11731416190, PreciControl Universal, for 4 x 3.0 mL or REF 06445918190, PreciControl Thyro Sensitive, for 4 x 2.0 mL
- REF 07299010190, Diluent MultiAssay, 36 mL sample diluent
- Anti-Tg assay, to verify the presence of antibodies to Tg in patient samples (e.g. Elecsys Anti-Tg assay, REF 07026919190)
- Distilled or deionized water
- General laboratory equipment
- **cobas e** analyzer

Additional materials for **cobas e** 402 and **cobas e** 801 analyzers:

- REF 06908799190, ProCell II M, 2 x 2 L system solution
- REF 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- REF 07485409001, Reservoir Cup, 8 cups to supply ProCell II M and CleanCell M
- REF 06908853190, PreClean II M, 2 x 2 L wash solution
- REF 05694302001, Assay Tip/Assay Cup tray, 6 magazines x 6 magazine stacks x 105 assay tips and 105 assay cups, 3 wasteliners
- REF 07485425001, Liquid Flow Cleaning Cup, 2 adaptor cups to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning Detection Unit
- REF 07485433001, PreWash Liquid Flow Cleaning Cup, 1 adaptor cup to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning PreWash Unit
- REF 11298500316, ISE Cleaning Solution/Elecsys SysClean, 5 x 100 mL system cleaning solution

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator’s manual for analyzer-specific assay instructions.

Resuspension of the microparticles takes place automatically prior to use.

Place the cooled (stored at 2-8 °C) **cobas e** pack on the reagent manager. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the **cobas e** pack.

Calibration

Traceability: This method has been standardized against CRM (Certified Reference Material) 457, of the BCR (Community Bureau of Reference) of the European Union.[25]

The predefined master curve is adapted to the analyzer using the relevant CalSet.

Calibration frequency: Calibration must be performed once per reagent lot using fresh reagent (i.e. not more than 24 hours since the **cobas e** pack was registered on the analyzer).

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Renewed calibration is recommended as follows:

- after 12 weeks when using the same reagent lot
- after 28 days when using the same **cobas e** pack on the analyzer
- as required: e.g. quality control findings outside the defined limits

Quality control

Use PreciControl Universal, PreciControl Thyro Sensitive or other suitable controls for routine quality control procedures.

Controls for the various concentration ranges should be run individually at least once every 24 hours when the test is in use, once per **cobas e** pack, and following each calibration.

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The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

If necessary, repeat the measurement of the samples concerned.

Follow the applicable government regulations and local guidelines for quality control.

Calculation

The analyzer automatically calculates the analyte concentration of each sample (either in ng/mL or µg/L).

Interpretation of the results

When interpreting the test results the possibility of anti-Tg antibodies in the sample should be taken into account. Results should be preferably verified by the determination of anti-Tg (e.g. Elecsys Anti-Tg assay).[1,2]

Limitations - interference

The effect of the following endogenous substances and pharmaceutical compounds on assay performance was tested. Interferences were tested up to the listed concentrations and no impact on results was observed.

Endogenous substances

Compound	Concentration tested
Bilirubin	≤ 1128 µmol/L or ≤ 66 mg/dL
Hemoglobin	≤ 0.373 mmol/L or ≤ 600 mg/dL
Intralipid	≤ 2000 mg/dL
Biotin	≤ 4912 nmol/L or ≤ 1200 ng/mL
Rheumatoid factors	≤ 600 IU/mL
IgG	≤ 2 g/dL
IgA	≤ 1.6 g/dL
IgM	≤ 0.5 g/dL

Criterion: For concentrations of 0.04-2 ng/mL the deviation is ≤ 10 %. For concentrations > 2 ng/mL the deviation is ≤ 25 %.

There is no high-dose hook effect at Tg concentrations up to 120000 ng/mL.

Pharmaceutical substances

In vitro tests were performed on 17 commonly used pharmaceuticals. No interference with the assay was found.

In addition, the following special drugs were tested. No interference with the assay was found.
Criterion: Recovery within ± 10 % of initial value.

Special drugs

Drug	Concentration tested µg/mL
Iodide	0.2
Carbimazole	30
Thiamazole	80
Propylthiouracil	300
Perchlorate	2000
Propranolol	240
Amiodarone	200
Prednisolone	100
Hydrocortisone	200
Fluocortolone	100
Octreotide	0.3
L-T3	0.5
D-T3	0.5
L-T4 (Levothyroxine)	5
D-T4	5

Drug interferences are measured based on recommendations given in CLSI guidelines EP07 and EP37 and other published literature. Effects of concentrations exceeding these recommendations have not been characterized.

In rare cases, interference due to extremely high titers of antibodies to analyte-specific antibodies, streptavidin or ruthenium can occur. These effects are minimized by suitable test design.

Tg determinations can be affected by the presence of anti-thyroglobulin antibodies (anti-Tg) or by non-specific effects in patient sera. Results should be preferably verified by the determination of anti-Tg (e.g. Elecsys Anti-Tg assay).[1,2]

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

Limits and ranges

Measuring range

0.04-500 ng/mL (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 0.04 ng/mL. Values above the measuring range are reported as > 500 ng/mL (or up to 5000 ng/mL for 10-fold diluted samples).

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 0.02 ng/mL

Limit of Detection = 0.04 ng/mL

Limit of Quantitation = 0.1 ng/mL

The Limit of Blank, Limit of Detection and Limit of Quantitation were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17-A2 requirements.

The Limit of Blank is the 95th percentile value from n ≥ 60 measurements of analyte-free samples over several independent series. The Limit of Blank corresponds to the concentration below which analyte-free samples are found with a probability of 95 %.

The Limit of Detection is determined based on the Limit of Blank and the standard deviation of low concentration samples. The Limit of Detection corresponds to the lowest analyte concentration which can be detected (value above the Limit of Blank with a probability of 95 %).

The Limit of Quantitation is the lowest analyte concentration that can be reproducibly measured with an intermediate precision CV of ≤ 20 %.

When reporting results below Limit of Quantitation a higher uncertainty needs to be taken into consideration.

Dilution

Samples with Tg concentrations above the measuring range can be diluted with Diluent MultiAssay. The recommended dilution is 1:10 (either automatically by the analyzers or manually). The concentration of the diluted sample must be ≥ 40 ng/mL.

After manual dilution, multiply the result by the dilution factor.

After dilution by the analyzers, the software automatically takes the dilution into account when calculating the sample concentration.

Expected values

3.5-77 ng/mL

These values correspond to the 2.5th and 97.5th percentiles of results obtained from a total of 478 healthy Caucasian subjects (254 males, 224 females).

Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.

Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using Elecsys reagents, samples and controls in a protocol (EP05-A3) of the CLSI (Clinical and Laboratory Standards

Institute): 2 runs per day in duplicate each for 21 days (n = 84). The following results were obtained:

cobas e 402 and **cobas e** 801 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean ng/mL	SD ng/mL	CV %	SD ng/mL	CV %
Human serum 1	0.147	0.003	2.2	0.005	3.2
Human serum 2	1.99	0.048	2.4	0.054	2.7
Human serum 3	39.4	0.556	1.4	0.720	1.8
Human serum 4	247	4.49	1.8	5.38	2.2
Human serum 5	485	7.51	1.6	9.28	1.9
PC[b)] Universal 1	23.2	0.353	1.5	0.444	1.9
PC Universal 2	84.6	0.982	1.2	1.24	1.5
PC Thyro Sensitive	1.00	0.014	1.4	0.019	1.9

b) PC = PreciControl

Method comparison

a) A comparison of the Elecsys Tg II assay, REF 08906564190 (**cobas e** 801 analyzer; y), with the Elecsys Tg II assay, REF 07027931190 (**cobas e** 801 analyzer; x), gave the following correlations (ng/mL):

Number of samples measured: 146

Passing/Bablok[26]	Linear regression
y = 1.03x - 0.021	y = 0.998x + 1.05
τ = 0.973	r = 0.998

The sample concentrations were between 0.056 and 495 ng/mL.

b) A comparison of the Elecsys Tg II assay, REF 08906564190 (**cobas e** 402 analyzer; y), with the Elecsys Tg II assay, REF 08906564190 (**cobas e** 801 analyzer; x), gave the following correlations (ng/mL):

Number of samples measured: 144

Passing/Bablok[26]	Linear regression
y = 1.01x - 0.010	y = 1.00x + 0.076
τ = 0.990	r = 1.00

The sample concentrations were between 0.054 and 490 ng/mL.

Analytical specificity

The following cross-reactivities were found, tested with thyroglobulin concentrations of approximately 5 and 50 ng/mL:

Cross-reactant	**Concentration tested**	**Cross-reactivity %**
TSH	1000 mIU/L	not detectable
TBG	200000 ng/mL	not detectable

References

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For further information, please refer to the appropriate user guide or operator's manual for the analyzer concerned, the respective application sheets and the Method Sheets of all necessary components (if available in your country).

Elecsys Tg II

A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

Any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.

The Summary of Safety & Performance Report can be found here: https://ec.europa.eu/tools/eudamed

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see navifyportal.roche.com for definition of symbols used):

CONTENT	Contents of kit
SYSTEM	Analyzers/Instruments on which reagents can be used
REAGENT	Reagent
CALIBRATOR	Calibrator
→	Volume for reconstitution
GTIN	Global Trade Item Number
Rx only	For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

CE 0123

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